

Operative and Postoperative Emergency Use of Hydrocortisone Derivatives and Corticotropin

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THE RESPONSE OF A PATIENT to major surgical operation is greatly jeopardized in the presence of adrenocortical impairment.

The most important biologically active steroids secreted by the adrenal cortex may clinically be divided into (1) glucocorticoids, of which hydrocortisone (17-hydroxycorticoid) is the most important, (2) 17-ketosteroids, derived from the adrenal glands in females and from both the adrenals and testes in males, (3) mineralo-corticoids, primarily electrolyte regulating hormones such as aldosterone, and (4) small amounts of estrogen and progesterone.

The urinary output of total 17-hydroxycorticoids reflects the status of overall adrenal cortical activity and ranges between 25 and 35 per cent of the adrenal output of these hormones. The urinary excretion of these steroids is expressed in milligrams of hydrocortisone per 24 hours and averages 7 ± 3 mg. in women and 10 ± 4 mg. in men as determined by the method of butanol extraction and a Porter-Silber color reaction.⁵

The output of hydrocortisone by normal adrenal glands is 25 to 30 milligrams per day. Under severe physical and emotional stress the adrenal output rises to 50 to 100 milligrams of hydrocortisone during the first 24 hours with a gradual decrease to normal in five to seven days (Chart 1).

The advent of more readily absorbable and more powerful adrenal hormone derivatives has facilitated adrenal replacement therapy.⁶ The physiological and pharmacological properties of these hormones that are of immediate interest to surgeons are (1) maintenance of life in cases of total adrenal insufficiency, (2) antihypotensive action, and (3) antiinflammatory and antiendotoxic properties.

PREPARATIONS AVAILABLE

Hydrocortisone hemisuccinate sodium is the therapeutic agent of choice in surgical emergencies. It is a water-soluble crystalline preparation (134 mg. is equivalent to 100 mg. of free hydrocortisone) available in a lyophilized form and may be dissolved

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• Impairment of adrenal function is a great hazard to patients undergoing major operation. The most important adrenal steroids are glucocorticoids (hydrocortisone), 17-ketosteroids, mineralo-corticoids (aldosterone), and small amounts of estrogen and progesterone. Urinary output of 17-hydroxycorticoids reflects overall adrenal cortical activity. Under severe stress this output increases greatly.

Adrenal replacement therapy is facilitated by the advent of more powerful and more soluble adrenal hormone derivatives. Hydrocortisone hemisuccinate sodium is the agent of choice in surgical emergencies and for management of bilateral adrenalectomy. Fatal adrenal crisis may develop during operation in patients receiving hydrocortisone for long periods of time. Hydrocortisone may be of help in unresponsive shock not due to loss of blood. The usual side effects of the corticoids can be controlled easily.

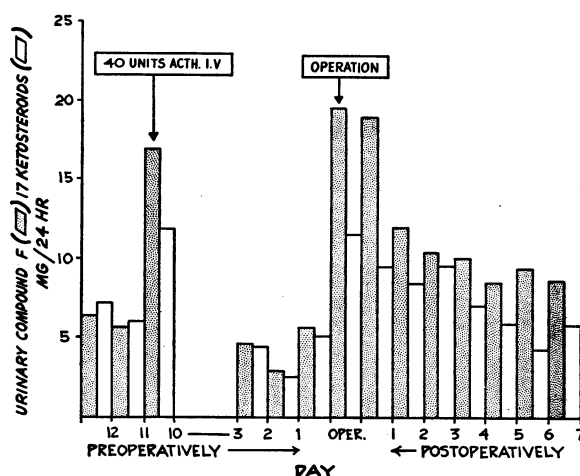


Chart 1.—Response of normal adrenal cortex to operation under general anesthesia (the patient a woman 43 years of age).

in 2 to 4 milliliters of saline solution. It is the only preparation* that can be administered intravenously or intramuscularly in doses of 100 mg. or more without infusion apparatus in order to obtain rapidly a high steroid blood level. It has a half-life of four to five hours and therefore should be administered every six to eight hours. In the presence of normal renal function rapid excretion of hydrocortisone

* Available at the time of this writing.

tisone prevents a cumulative effect. The hormone is available in vials of 100 mg.

Hydrocortisone (free-alcohol) is available for addition to intravenous fluids in ampules containing 100 mg. in 20 ml. of 50 per cent alcohol solution. It is added to 500 ml. of 5 per cent dextrose in water prior to use. Its eosinopenic effect and other biological properties are essentially similar to those of hydrocortisone hemisuccinate sodium. However, the small quantity of diluent required for administration makes the hemisuccinate the agent of choice in extreme emergencies. Hydrocortisone (free-alcohol) is also available in tablet form in doses of 5, 10 and 20 mg. for oral use and as the acetate for intraarticular injection.

Prednisolone is the agent of choice in prolonged corticoid therapy because its antiinflammatory activity is three to four times that of hydrocortisone with less sodium-retaining effect and potassium loss in equivalent effective doses. It is available as 1, 2, 2.5, and 5 mg. tablets for oral use and various injectable forms are being made available.

Corticotropin (ACTH) is available in three forms: (a) as lyophilized powder, 10 to 40 units per vial for intramuscular or intravenous use as an aqueous solution, (b) as a long-acting (12 to 24 hours) gel containing 40 to 80 clinical units per milliliter, and (c) as zinc corticotropin 40 to 80 units per milliliter with a 24-hour-to-48-hour action depending upon the dosage. The gel preparations may be added to 5 per cent dextrose in water for intravenous use if the lyophilized preparations are not available.

In emergency situations corticotropin should *not* be used in adrenal insufficiency with severe hypopituitarism or following adrenal cortical suppression by prolonged steroid administration, because a responsive adrenal cortex is essential for corticotropin to be effective rapidly.³

SPECIAL USES

1. *Management of bilateral adrenalectomy:* The rapid absorption of hydrocortisone hemisuccinate sodium permits the surgeon to dispense with the preoperative administration of steroids before removal of both adrenal glands. It is given in doses of 100 mg. intramuscularly during induction of anesthesia and at regular intervals thereafter as indicated in Table 1. This regimen was used for 26 patients who had bilateral adrenalectomy for metastatic breast carcinoma at the University of California Hospital, and there were no postoperative deaths.

The following is a report of an illustrative case:

A 38-year-old woman underwent bilateral oophorectomy and adrenalectomy for metastatic breast carcinoma. Adrenal replacement therapy consisted of administration of 100 mg. of hydrocortisone

TABLE 1.—Steroid Replacement Therapy

Day of operation:

HHS (hydrocortisone hemisuccinate sodium)
100 mg. intramuscularly at the time of incision
50 mg. intramuscularly 4 hours after initial dose
50 mg. intramuscularly every 6 hours thereafter

First postoperative day:

HHS (hydrocortisone hemisuccinate sodium)
50 mg. intramuscularly every 8 hours

Second postoperative day:

HHS (hydrocortisone hemisuccinate sodium)
25 mg. intramuscularly every 6 hours

or

Cortisone acetate
25 mg. every 6 hours orally

Third postoperative day:

Cortisone acetate
25 mg. every 8 hours orally

DCA (desoxycorticosterone acetate)
2 mg. intramuscularly if no edema or heart failure
Begin weighing patient daily

Fourth postoperative day:

Cortisone acetate
12.5 mg. every 6 hours orally

DCA (desoxycorticosterone acetate)
2 mg. intramuscularly

Fifth postoperative day:

Cortisone acetate
12.5 mg. every 8 hours orally

Sixth through tenth postoperative days:

DCA, long-acting (desoxycorticosterone trimethylacetate)

hemisuccinate sodium intramuscularly at the time of incision, followed by 50 mg. intramuscularly six hours later, and then 25 mg. every six or eight hours until the patient was able to take cortisone acetate orally. Blood pressure was maintained at a satisfactory level and the patient made an uneventful recovery.

2. *Management of adrenal insufficiency secondary to prolonged steroid administration:* Patients who have been given hydrocortisone or its derivatives for long periods may develop a severe or fatal adrenal crisis during or after operation.⁴ This crisis is characterized by pronounced hypotension refractory to the usual antishock measures such as blood and fluid replacement and administration of hypertensive agents. The usual maintenance dose of steroids adequate to control the disease under treatment may not be adequate to control surgical stress. Previous therapy with corticoids up to six months before operation may leave a patient without adequate adrenal cortical response to severe stress. The current wide use of steroids makes it imperative that every surgical history include an inquiry into whether the patient has previously been given any of them.

Adrenal insufficiency is best demonstrated by

comparing changes in urinary or plasma 17-hydroxycorticoids before and after stimulation by corticotropin.¹ Normal subjects show a three-fold to five-fold rise over control values of 24-hour urinary corticoid output following an eight-hour intravenous infusion of corticotropin. The fall in circulating eosinophils occurring four hours after an intramuscular injection of corticotropin is an easier, although less accurate, method of determining adrenocortical response. A decrease of less than 50 per cent usually indicates adrenal cortical insufficiency.

In patients with debilitating diseases of long duration, adrenal crises can be prevented by the administration of hydrocortisone before and for a few days after operation. This is best achieved by giving hydrocortisone hemisuccinate sodium as outlined in Table 1. For illustration:

A 54-year-old man with intractable ulcerative colitis had been treated with cortisone and hydrocortisone with only slight subjective improvement. He continued to have severe diarrhea and to lose weight. Six days before operation use of hydrocortisone was discontinued and administration of corticotropin was begun to stimulate the suppressed adrenal glands. Colectomy was done and at operation a pronounced decrease in blood pressure occurred which was unresponsive to administration of whole blood or vasopressor drugs. Normal blood pressure was promptly restored upon intravenous administration of hydrocortisone (Chart 2).

3. *Use as antihypotensive agents:* The use of intravenous or intramuscular hydrocortisone may be of great help in the treatment of unresponsive shock not due to blood loss. Use of this hormone in cases where no definite adrenal cortical insufficiency can be demonstrated may be justified by its apparent ability to potentiate the action of vasoconstrictors.² For illustration:

A 30-year-old woman underwent cardotomy for correction of a mitral valve defect. During the second postoperative day a progressive decrease in blood pressure occurred. The pressure did not respond to large doses of vasopressor drugs. The administration of 100 mg. of hydrocortisone intravenously resulted in prompt return of blood pressure to normal levels. The dosage of hydrocortisone was gradually decreased during the next four days (Chart 3).

PRECAUTIONS

The use of large doses (over 100 mg. daily) of hydrocortisone may bring about undesirable side effects such as:

1. Impairment of ability to localize infections. The presence of tuberculosis is therefore an absolute contraindication to the use of steroids.
2. Fibroblast proliferation may be retarded with subsequent impairment of wound healing. This is

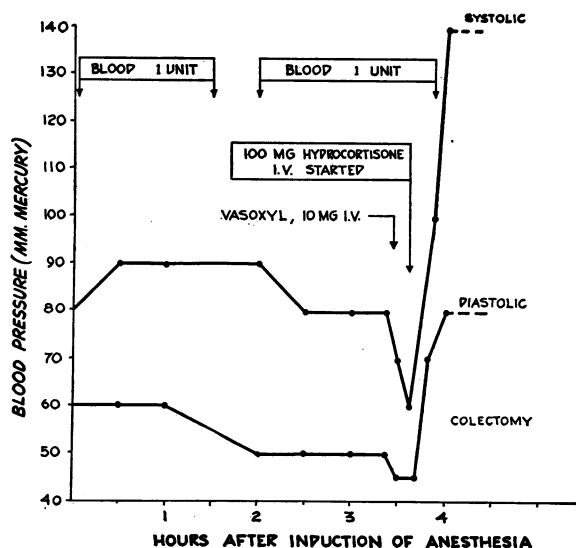


Chart 2.—Blood pressure changes following administration of hydrocortisone to 54-year-old man during colectomy.

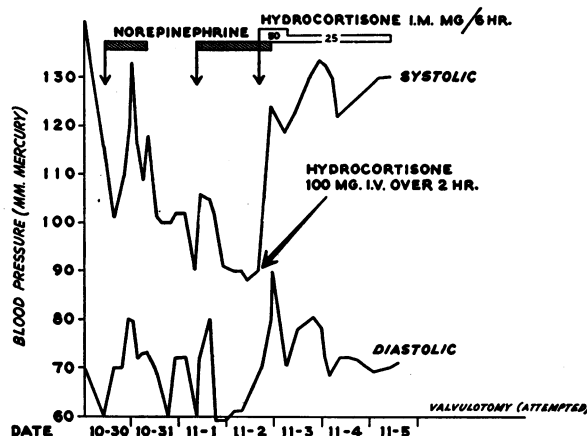


Chart 3.—Use of hydrocortisone intramuscularly and intravenously for shock after failure of vasopressor drug. The patient was a woman 30 years of age upon whom valvulotomy was attempted.

not a serious problem where treatment does not exceed a week in duration.

3. Sodium retention and potassium loss may predispose to edema and hypertension. Malignant hypertension is a contraindication to the use of corticoids.

4. Aggravation of psychosis or epilepsy.

5. Hyperglycemia and glycosuria occasionally occurs and is easily controlled by insulin.

6. Increased secretion of hydrochloric acid by the gastric mucosa makes the presence of a peptic ulcer a contraindication to the use of corticoids.

7. Negative nitrogen balance may occur and thus increase azotemia.

The usual side effects can be easily controlled. Gain in weight due to sodium and water retention can be counteracted by reducing sodium intake and by giving potassium chloride enteric-coated tablets, 1 to 3 gm. three times daily. A high protein diet will help control negative nitrogen balance. If hypertension continues despite salt restriction and diuretic measures, the dosage of hydrocortisone should be reduced or antihypertensive drugs tried.

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